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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/826,113	04/16/2004	Piotr Chomczynski	CNA / 19	1054

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EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	**PAPER NUMBER**
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/826,113	CHOMCZYNSKI, PIOTR	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29-39,41,44,46-52 and 59-63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *40,62 and 63* is/are allowed.

6)☒ Claim(s) *29-39,41,46-52 and 59-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 20, 2007 has been entered.objection to claim 44 is withdrawn in view of the amendment.

Claim Interpretation

2. Prior to application of the art, the scope and content of the claims must be analyzed. In this case, the new limitation to require "a buffer at a concentration sufficient to maintain a pH in the range from about pH 3.6 to below pH 4.0" does not provide any specific requirements for the buffer. Therefore, any amount of buffer will function to maintain the pH in the desired range when the sample is already in the desired range. Consequently, this limitation does not necessarily impose any limitation on the claim other than the presence of a component with even minimal buffering capacity. For purposes of compact prosecution, both anticipatory and obviousness rejections will be made over this limitation, in order to fully address the limitation.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 29-39, 41, 46, 52 and 59-61 are rejected under 35 U.S.C. 102(b) as being anticipated by Chen et al (Chinese patent 1,220,995, translation).

The rejection is based upon a translation of the Chen et al patent, which is attached.

Chen teaches a *method for isolating purified RNA from a biological sample* of claims 29 and 59 (see page 3, bottom half, for example or page 4) comprising:

a) *treating the sample comprising phenol at a final concentration ranging from about 10% w/w to about 60% w/w and at least one ribonuclease inhibitor* (see page 6, where 12-46% phenol is used in conjunction with guanidine isothiocyanate, an RNAse inhibitor and see page 8, preferred embodiment 2, step 1, where the phenol reagent with 30% w/w is added to the tissue),

b) mixing the sample with at least one hydrophobic solvent and a buffer at a concentration sufficient to maintain a pH in the range from about pH 3.6 to below pH 4.0 (see page 8, preferred embodiment 2, where the pH of the phenol reagent is pH 3.5, which is about 3.6 and where the hydrophobic solvent chloroform/isoamyl alcohol is added to the solution. Further note that Chen teaches overlapping ranges of pH from 3.5 to 6.5 and the use of glacial acetic acid to regulate the pH value (see page 3)),

c) recovering the purified RNA from an aqueous phase to which about an equal volume of a water soluble organic solvent is added to precipitate the purified

RNA (See page 8, preferred embodiment 2, where the aqueous phase is precipitated with isopropanol),

d) washing and solubilizing the precipitated RNA (see page 9, where the RNA precipitate is washed with alcohol and dissolved in a buffer).

With regard to claim 30, Chen teaches the use of acetate and citrate buffers (see page 8, preferred embodiment 2, lines 3 and 4).

With regard to claims 31-34, Chen teaches the use of ribonuclease inhibitors (see page 8, preferred embodiment 2, line 1, where the chaotropic salt guanidine isothiocyanate is used as an RNAse inhibitor at a concentration in the range of 0.5 M to about 6M).

With regard to claims 35-36, Chen teaches the use of detergents such as SDS and sarcosine including a range of 0.1% SDS (see page 8, preferred embodiment 2, lines 2-3).

With regard to claims 37-39, Chen teaches the use of sodium acetate and trisodium citrate, where claim 38 indicates that acetate is a preferred salt and claim 39 indicates that citrate is a preferred chelating agent).

With regard to claim 41, Chen teaches the use of Guanidine salts (see page 8, line 1).

With regard to claims 46, Chen teaches a pH range of 3.5-6.5 and exemplifies a pH of 3.5 (see page 3 and see page 8, preferred embodiment 2).

With regard to claim 52, 60, 61, Chen teaches precipitation with isopropanol (see page 8).

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claim 29-39, 41, 46, 52 and 59-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al (Chinese patent 1,220,995, translation) in view of Chomczynski (U.S. Patent 5,346,994).

Chen teaches a *method for isolating purified RNA from a biological sample* of claims 29 and 59 (see page 3, bottom half, for example or page 4) comprising:

a) *treating the sample comprising phenol at a final concentration ranging from about 10% w/w to about 60% w/w and at least one ribonuclease inhibitor* (see page 6, where 12-46% phenol is used in conjunction with guanidine isothiocyanate, an RNAse inhibitor and see page 8, preferred embodiment 2, step 1, where the phenol reagent with 30% w/w is added to the tissue),

b) mixing the sample with at least one hydrophobic solvent and a buffer at a concentration sufficient to maintain a pH in the range from about pH 3.6 to below pH 4.0 (see page 8, preferred embodiment 2, where the pH of the phenol reagent is pH 3.5, which is about 3.6 and where the hydrophobic solvent chloroform/isoamyl alcohol is added to the solution. Further note that Chen teaches overlapping ranges of pH from 3.5 to 6.5 and the use of glacial acetic acid to regulate the pH value (see page 3)),

c) recovering the purified RNA from an aqueous phase to which about an equal volume of a water soluble organic solvent is added to precipitate the purified RNA (See page 8, preferred embodiment 2, where the aqueous phase is precipitated with isopropanol),

d) washing and solubilizing the precipitated RNA (see page 9, where the RNA precipitate is washed with alcohol and dissolved in a buffer).

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With regard to claim 41, Chen teaches the use of Guanidine salts (see page 8, line 1).

With regard to claims 46, Chen teaches a pH range of 3.5-6.5 and exemplifies a pH of 3.5 (see page 3 and see page 8, preferred embodiment 2).

With regard to claim 52, 60, 61, Chen teaches precipitation with isopropanol (see page 8).

While Chen teaches the use of a pH adjusting component, Chen does not state that the amount used will be sufficient to maintain pH.

Chomczynski teaches the use of a pH adjusting component in an RNA solvent solution where "the solvent solution may include a buffering component, such as sodium acetate or sodium citrate, in an amount sufficient to maintain the pH of the solution (see column 3, lines 17-22)."

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the isolation buffer of Chen, who notes a desire to "regulate the pH value (see page 3)", to incorporate enough buffering component as taught by Chomczynski since Chomczynski notes "the solvent solution may include a buffering component, such as sodium acetate or sodium citrate, in an amount sufficient to maintain the pH of the solution (see column 3, lines 17-22)." An ordinary practitioner would have been motivated to include sufficent buffering in the isolation buffer of Chen in order to maintain the pH since both Chen and Chomczynski teach and motivate the use of buffering components to maintain the pH of the solution.

7. Claim 48-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al (Chinese patent 1,220,995, translation) in view of Focus (1998) 20(2):36.

Chen teaches the limitations of claims 29-39, 41, 46, 52 and 59-61 as discussed above. Chen further teaches, with regard to claims 48-49, the steps of:

a) treatment with the monophase reagent comprising phenol in concentrations from 12-46% w/w (see page 6) with a pH from 3.5-6.5 (see page 3) and a chaotrope (see page 6 where guandine isothiocyanate is used),

b) sedimenting the sample to obtain a purified sample substantially free of DNA, proteins and cellular components(see page 8, where the step of centrifugation is a form of sedimentation that will remove DNA, proteins and cellular components),

c) adding to the purified sample about an equal volume of a water soluble organic solvent to precipitate the purified RNA (See page 8, preferred embodiment 2, where the aqueous phase is precipitated with isopropanol),

d) sedimenting the precipitated RNA (see page 8, last sentence),

e) washing and solubilizing the precipitated RNA (see page 9, first five sentences).

With regard to claim 50, Chen teaches the use of chloroform (see page 8, middle of the page).

With regard to claim 51, Chen teaches addition of a composition which can be at "about 1.5 X" concentration (see page 8).

Chen does not teach sedimenting the sample prior to the addition of the phase separation agent.

Focus teaches that an intermediate centrifugation step, prior to the addition of chloroform, will remove undesired polysaccharides and genomic DNA.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the isolation buffer of Chen to perform an intermediate sedimentation step prior to addition of chloroform since Focus notes in response to the problem in RNA isolation with Trizol reagent (a reagent similar to Chen's except for the pH) that "If my tissue has a high content of proteoglycans and/or polysaccharides, what can I do to ensure that these compounds don't contaminate the RNA? (see page 36)" and the Focus response is "Centrifuge following homogenization before adding chloroform at 12,000 x G at 4 C (see page 36)". An ordinary practitioner would have been motivated to perform this centrifugation since Focus notes that the centrifugation will "pellet polysaccharides (also pellets genomic DNA)", so that the centrifugation step will enhance the purity and separation of the RNA from contaminating genomic DNA, as desired by Chen.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

> art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 47-51 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

As MPEP 2163.06 notes " If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen , 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)."

Here, the new claim limitation of "without adding a hydrophobic organic solvent to induce phase separation" is apparently new matter. The examiner careful reviewed the cited page of the specification. However, a statement at page 11, line 19, that isolation can occur "without performing phase separation" does not support the claim, which is drawn to the negative limitation of not adding a "hydrophobic organic solvent". While the express language at page 11, line 19, would support language such as "without performing phase separation", there is no support in the specification for the specific exclusion of "hydrophobic solvents" in the method. This is particularly clear in that all of Applicant's examples add bromochloropropane to the homogenates, which is a hydrophobic organic solvent (see page 20, lines 1-2, for example). As noted by MPEP 2173.05(I),

> " Any negative limitation or exclusionary proviso must have basis in the original disclosure. See Ex parte Grasselli , 231 USPQ 393 (Bd. App. 1983) aff'd mem., 738 F.2d 453 (Fed. Cir. 1984). The mere absence of a positive recitation is not basis for an exclusion. Any claim containing a negative

limitation which does not have basis in the original disclosure should be rejected under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement."

Since no basis has been found to support the new claim limitation in the specification, the claims are rejected as incorporating new matter.

Allowable Subject Matter

10. Claims 40, 62 and 63 are allowed.

11. The following is a statement of reasons for the indication of allowable subject matter: Claims 40, 62 and 63 are drawn to the use of particular phenol derivatives or particular organic compounds in the RNA isolation buffer. The search did not identify any prior art which taught or suggested the use of the specific chemical compounds listed in RNA (or nucleic acid) isolation. With regard to claim 44, while Puissant teaches the pretreatment step with Guanidine, Puissant never suggests a pH of less than 4.0.

Response to Arguments

12. Applicant's arguments filed April 20, 2007 have been fully considered but they are not persuasive.

Applicant repeats the argument that "substantially free" should exclude teh method of Chen. As noted previously, the term "substantially free" does not provide specific limits on the amount of RNA that can be present, and therefore the prior art of Chen is properly applicable.

Applicant then argues that Chen lacks enough pH regulator to meet a claim to "sufficient to maintain pH". This argument is not persuasive for several reasons. First, the argument presupposes that the sample will have a pH that is different enough to

overcome the buffering capacity of the Chen component. However, there is no pH requirement for the sample and the sample may have the same pH as that of Chen, resulting in sufficient buffering capacity in the reagent of Chen. Second, the term "sufficient" is extremely broad and encompasses the expressly taught pH regulator of Chen. Finally, in order to fully address the claim, both 102 and 103 rejections were made in order to demonstrate that even if a reviewing body found Chen was not properly anticipatory, the substitution of more buffering capacity in an RNA analysis reagent is prima facie obvious.

Applicant then argues the new limitation of "without adding a hydrophobic organic solvent to induce phase separation". This limitation does overcome the Chen reference on prior art grounds for claim 47. However, as noted above, the specification does not support this generic version of the claim. Further, for claim 48, the impact of this limitation is entirely eliminated by step c), which expressly teaches addition of the chloroform to the sample. Claims 48-51 do not require that the step (b) do any thing other than sediment, which is taught in the new 103 rejection using the Focus reference.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jeffrey Fredman
Primary Examiner
Art Unit 1637
5/9/07